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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,819	04/30/2001	Tomoko Nakayama	P107424-00027	9941

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RADER FISHMAN & GRAUER PLLC
LION BUILDING
1233 20TH STREET N.W., SUITE 501
WASHINGTON, DC 20036

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/843,819	NAKAYAMA ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the appeal brief filed on 9/9/2003, PROSECUTION IS HEREBY REOPENED. A new grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 1-11 are still pending. All rejections not reiterated herein are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Non-Final**.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 2 is indefinite over the recitation of "nucleic acid inclusion body." The term "nucleic acid inclusion body" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes a nucleic acid inclusion body. It is unclear, e.g. whether the phrase refers to any body in its entirety, comprising nucleic acids(i.e. an entire animal or plant), or to an isolated sample from just a specific organ/tissue type comprising nucleic acids, or to a single cell comprising nucleic acids, or even just to a purified nucleic acid harvested from one of these three sources prior to amplification...etc. The claims should be amended to clarify what specific sample types are included in the "nucleic acid inclusion body" category.

B. Claim 3 is indefinite over the recitation of "and/or" located between the two steps of adjusting a pH value. It is unclear if both the 25°C step and 70°C step occur in independent reactions, sequentially, singly, multiply, or multiply in sequence. As a result, it is unclear at which point of the reaction and at what frequency pH adjustments occur.

Appropriate correction is required.

Response to Arguments:

1. With respect to claim 2, appellants' assertion that the term "nucleic acid inclusion body" is clear on it face is acknowledged. However, the examiner maintains that the claim is still drawn to indefinite subject matter as it is not clear to what the phrase is attempting to be directed. It is not clear if the nucleic acids are including a body, if a body is including the nucleic acids, and in either instance, what a body is meant to connote; a body of an animal, a cell body, an

encapsulated mass of nucleic acids. Although the examiner acknowledges its repeated use in the specification, nowhere in the specification does the context ameliorate the claim's indefiniteness.

2. With respect to claim 3, appellants' assertion that "it is quite clear from the claim, when taken in context, is proper construction, and clear on its face" is noted. However, the examiner maintains that the claiming of each scenario in the alternative remains indefinite. For example, it is not clear if the first pH requirement is to be fulfilled before the amplification reaction begins, during the reaction, before a certain step(elongation, denaturation, etc), or following the termination of the PCR program. Likewise, it is similarly indefinite if the second pH requirement is meant to follow the extension portion of an amplification reaction, follow the 25 degree portion of the reaction, not be performed if the 70 degree portion precedes the 25 degree portion. The presence of the "and/or" makes indefinite the two requirements to change the pH as neither their context in the claims or specification clarifies the limitation.

-----THE FOLLOWING ARE NEW GROUNDS OF REJECTION-----

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant should note that in light of the indefiniteness rejections still standing on claims 2 and 3, the examiner has applied the art as best as she saw fit to apply to her interpretation of the currently indefinite claims.

2. Claims 1-9 and 11, are rejected under U.S.C. 103(a) as being unpatentable over Ivanov et al. (US Patent 6,183,998 filed October 31st 1998).

Ivanov et al. teach a method for synthesis of nucleic acids to amplify an intended nucleic acid region in which a content of guanine (G) and cytosine (C) is rich, wherein an aliphatic polyhydric alcohol, glycerine(aka glycerol) is present in an amplification reaction solution as well as a reaction with ammonium sulfate present. Ivanov et al. teach "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture. For example, difficult PCR amplification, such as reaction that yield non-specific products, and especially amplification of templates having a high GC content or having extensive secondary structure, may be improved by employing additives that 'isostabilize' AT- and GC-base pairing to the level of AT-base pair stability."(Column 8 lines 11-18). The reference goes on to teach that suitable additives that can be used to this end of amplifying high GC content sequences include "most preferably glycerol" and also "most preferably ammonium sulfate"(Col. 8 lines 20 and 25). Ivanov et al. do not specifically exemplify as a single embodiment a method in which the synthesis of nucleic acids is performed in the presence of both glycerol and

ammonium sulfate. However, in view of the fact that Ivanov teaches that amplification reactions should be performed in the presence of additives such as glycerol or ammonium sulfate, it would have been obvious to one of ordinary skill in the art at the time the invention was made to performed the amplification method of Ivanov using a reaction mixture that contained both glycerol and ammonium sulfate in order to have achieved the expected benefit expressly stated by Ivanov, of improving the specificity of the amplification method. As discussed in MPEP 2144.06-2144.07, it is *prima facie* obvious to combine two reagents which are taught in the prior art to be useful for the same purpose and to use these reagents in combination based on their known functions. It is noted that Ivanov (column 8) teaches that "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture." And, Ivanov teaches that glycerol and ammonium sulfate are equivalents in that they both serve to "iso-stabilize" AT and GC- base pairing to the level of AT-base pairing stability.

With respect to claim 2, the reference teaches the above method of synthesis of nucleic acids wherein the nucleic acids to be amplified, come from a nucleic acid inclusion body such as cells from a HeLa human cell line in example 15,(Col. 17) or from a living body derived sample itself such as human blood as taught in examples 7 and 8(Col. 11 and 12 respectively).

With respect to claim 3, the reference teaches that "in order to release the primer extension activity of Taq DNA polymerase" a reaction mixture of 40 ul containing various reagents(See col. 10 lines 43-45) and "10mM Tris HCl pH 8.8 at 25 °C" was prepared(Col. 10 lines 40-47). Additionally the reference meets the second/alternate limitation in claim 3 through its teaching of a reaction solution that has the pH of 8.4 as it is carried through an amplification

reaction that encounters an extension step at about 70°C(72 °C) as is taught in Example 8, Col. 12, lines 55-65).

With respect to claims 4 and 5, the reference teaches multiple sequences wherein the GC content in the GC rich region is both more than 40% and in the range of 50% to 70%. The reference teaches for instance the amplification of a 831bp PCR fragment of the human glycerinaldehyde-3-phosphate-dehydrogenase gene(Example 15, Col 16-18) with SEQ ID NO: 8 and 9. The resulting amplified fragment is 55% GC rich(459/831bp)(Please see attached alignments of SEQ ID NOS 8 and 9 to the human glycerinaldehyde-3-phosphate-dehydrogenase gene sequence provided).

With respect to claims 6-8, the reference teaches the above method of nucleic acid synthesis wherein the additive is a polyhydric alcohol that is an aliphatic polyhydric alcohol, glycerin(glycerol)(Col. 8 line20). Furthermore the reference teaches the method using the additive of polyethylene glycol(Col. 8 lines 26-27).

With respect to claims 9 and 11 both limitations of glycerin/glycerol being present from 2.5% to 20% by volume in the amplification solution and the second wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution are taught in Col. 8's teaching of reaction parameters. Ivanov et al. teaches that the "PCR additives are advantageously added to a PCR reaction mixture in an amount effective to improve the specificity of the amplified product. Typically concentrations of additive from 1mM to 5M, preferably about 1M, are used, however any amount that improves the yield of the specific amplification product, compared with a PCR reaction carried out in the absence of the additive, is suitable"(Col. 8 lines 37-41).

3. Claim 10 is rejected under U.S.C. 103(a) as being unpatentable over Ivanov et al. (US Patent 6,183,998) in view of Yamada et al. or Kelly et al. or Holliger et al. or Ukachi et al. or Endo et al. or Taniguchi et al. (respectively US Patents 5,369,096; 4,978,757; 4,820,309; 4,683,280; 4,368,314; 6,054501).

The teachings of Ivanov et al. can be reviewed from above, but do not teach the limitation of claim 10 wherein the additive is ethylene glycol.

However, Yamada et al., or Kelly et al., or Holliger et al., or Ukachi et al., or Endo et al., or Taniguchi et al., each teach the use of polyethylene glycol to be equivalent to that of ethylene glycol. Especially US Patent, 5,369,096, Yamada et al. teach a reaction scheme in which polyethylene glycol is used interchangeably with ethylene glycol(See Columns 7-8,compound(6)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to replace the polyethylene glycol of Ivanov et al. with the ethylene glycol embodied in claim 10 of the present application with the expected benefit that the chemical would function the same as the polyethylene glycol in the Ivanov et al. reference as taught by the six cited patents.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number until 1/13/2004 is (703) 306-0284 and 1/14/2004 and after will be (571)272-0748. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

11/20/03

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER